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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/811,130	DEVARAJAN ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-11,24,26-28 and 30-46* is/are pending in the application.

4a) Of the above claim(s) *6,8,24,26,27 and 41-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,9-11,28,30-40 and 46* is/are rejected.

7)☒ Claim(s) *2-5, 9-11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :10/18/04, 11/3/04, 11/28/05, 7/24/06, and 11/16/06 .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-5 and 28-29, drawn to a method of detecting renal tubular cell injury, in the reply filed on 3/12/07 is acknowledged. The traversal is on the ground(s) that it would not constitute a serious burden to search and consider all inventions (see page 12 and 14). This is not found persuasive because the record as set forth in the previous Office action clearly shows that the searches of the various inventions are not co-extensive as a result of the particular limitations and method steps recited in the inventions as claimed and as shown by their different classification (see the previous Office action at pages 3-4).

Applicant further argues (see page 13) with respect to Groups I and II that the inventions appear to have the same function, namely detection of NGAL in urine. This is not found persuasive because the functions and effect of the inventions ***as claimed*** are distinct. Applicant argues that no reasoning for this assertion was given; however, distinctness of function and effect is clearly evident from the preambles of independent claims 1 and 6: Group I is a method for *detecting or diagnosing renal tubular cell injury*, while Group II is a method for *monitoring the effectiveness of a treatment*. As such, the purpose of the method of Group I is to detect or diagnose injury, and the method has the effect of determining whether the subject has the injury. The purpose of the method of Group II is to monitor the effectiveness of the treatment, and the outcome is a determination of whether a treatment has been effective.

Applicant further argues (see page 13) that the patient populations in the methods of Groups I, II, and IV appear not to be mutually exclusive as argued, but has not pointed to any

language in the specification or claims in support of this argument. In particular, Applicant's arguments appear to be directed more to the general nature of the invention and not to the inventions as claimed. Furthermore, the test for whether related inventions are mutually exclusive, or not overlapping in scope, is if a first invention would not infringe a second invention, and the second invention would not infringe the first invention. See MPEP 806.05. It is maintained for reasons of record that the inventions as claimed are drawn to related but patentably distinct processes, since there is nothing in the claims as written that would require (for example) the same patient population, such that performing the diagnostic method of Group I would not infringe the method of monitoring the effectiveness of treatment of Group II, and vice versa.

Applicant further argues (see page 13, last paragraph) that the inventions literally overlap in scope in that claim 6 (Group II) and claim 24 (Group IV) both incorporate the generic method of claims 1, 30, and 46 by detecting the presence of the biomarker NGAL in the urine sample. This is not found persuasive because as noted above, the test for whether related inventions are overlapping in scope is not whether they happen to share certain process steps or limitations in common, but rather if the inventions would infringe each other. It is noted that claims 1 and 46 are not drawn simply to methods of detecting NGAL in urine, but rather to diagnostic methods of "detecting renal tubular cell injury". The methods of Groups II and IV do not encompass such subject matter, and therefore, performing the method of Group I would not infringe either of the methods of Groups II or IV. Likewise, monitoring the effectiveness of a treatment as in Group II would not infringe the method of diagnosis of Group I.

Similarly, Applicant argues with respect to the restriction between inventions (I and II) and IV that all of the claims require the antibody detection step of Group I (see page 14), which is not found persuasive because Group IV does not recite a step involving antibody detection. Furthermore, the inventions as claimed differ in function and effect as evidenced by their preambles, in that Group I is a diagnostic method for detecting a renal tubular cell injury, Group II is a method for monitoring the effectiveness and treatment, and Group IV is a method for identifying the extent of an injury. As such, it is maintained for reasons of record that the inventions are drawn to related but patentably distinct processes.

Applicant further argues that the "event" causing renal tubular cell injury as in Group IV may be the same as the "treatment" for renal tubular cell injury as in Group II, and that therefore, the inventions overlap in scope (page 14). In particular, Applicant refers to the specification at paragraph 42, which indicates that events causing renal tubular cell injury may include administration of pharmaceuticals such as nephrotoxins. This is not found persuasive because Group II relates to a "treatment ***for the renal tubular cell injury***" and not to any "treatment" *per se*. Although the specification administration a nephrotoxin might be considered a "treatment" for some disease condition, there is nothing in the specification to indicate that nephrotoxins would be considered treatments *for renal tubular cell injury* according to the claimed invention (and indeed, this would seem to be counterintuitive).

Applicant further argues (page 14) that each of claims 1, 30, 46, 6 and 24 "would appear to be capable of being used together, as lacking a materially different design, mode of operation, function or effect." Applicant's remarks are not fully understood. It appears that Applicant acknowledges that the inventions of Groups I-II and IV lack a materially different design, mode

of operation, function or effect, as was contended by the Office. The argument that the inventions "would appear to be capable of being used together" is not persuasive, since distinctness of related processes may be shown **either** by a showing that the inventions are not capable of use together **or** by a showing that the processes have a materially different design, mode of operation, function, or effect. The record as set forth in the previous Office action demonstrates the latter, namely, that the inventions of Groups I-II and IV are distinct because they differ in function and effect.

Applicant's arguments as they pertain to the overlapping scope of newly added claim 30 are acknowledged (see pages 13-14) but are moot because this claim will be treated under linking claim practice (see below) and not as a related process.

The requirement is still deemed proper and is therefore made FINAL.

The claim amendments of 3/12/07 are acknowledged. Claims 1-6, 8-11, 24, and 27-28 were amended. Claims 7, 12-23, 25, and 29 were canceled. New claims 30-46 have been added.

Linking Claim Practice

2. Newly added claim 30 link(s) inventions I, II, and IV. Specifically, it is noted that independent claim 30 recites a method for "**evaluating the renal tubular cell injury status**", which is broader in scope than the elected invention (Group I, drawn to a **method for detecting renal tubular cell injury**) and would also encompass the non-elected inventions drawn to methods for monitoring the effectiveness of treatment (Group II) as well as methods for

identifying the extent of a renal tubular cell injury (Group IV). See especially claim 39. As such, newly added claims 30-40 and 46 will be examined along with the elected invention according to linking claim practice (see MPEP 809).

3. The restriction requirement among the linked inventions is **subject to** the nonallowance of the linking claim(s), claim 30. Upon the indication of allowability of the linking claim(s), the restriction requirement as to the linked inventions **shall** be withdrawn and any claim(s) depending from or otherwise requiring all the limitations of the allowable linking claim(s) will be rejoined and fully examined for patentability in accordance with 37 CFR 1.104 **Claims that require all the limitations of an allowable linking claim** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

Applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, the allowable linking claim, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

4. Applicant's reply states that claims 1-5, 9-11, and 31-46 read on the elected invention of Group I. however, the Examiner has determined that newly submitted **claims 41-45** do not read on the elected invention, for the following reasons:

Applicant's elected invention is a method for detecting or diagnosing renal tubular cell injury. Claims 41-45 depend from linking claim 30, which recites a method for "evaluating the renal tubular cell injury status".

However, dependent claims 41-43 clearly relate to the non-elected invention of Group IV, which is a method for **identifying the extent of a renal tubular cell injury** (see especially claim 41, which refers to "the extent of the renal tubular cell injury").

Furthermore, dependent claims 44-45 clearly relate to the non-elected invention of Group II, which is a method for **monitoring the effectiveness of a treatment**. See especially claim 45, which refers to "determining...if the treatment has been effective", and Applicant's reply at page 11, which indicates that the method is carried out following treatment.

Accordingly, claims 41-45 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

5. Claims 6, 8, 24, 26-27, and 41-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/12/07 as discussed above.

Status of the Claims

6. Claims 1-6, 8-11, 24, 26-28, and 30-46 are pending in the application, with claims 6, 8, 24, 26-27, and 41-45 currently withdrawn. Claims 1-5, 9-11, 28, 30-40, and 46 are subject to examination below.

Manner of making amendments in applications

7. In the interest of expediting prosecution, the amendment of 3/12/07 has been accepted. However, Applicant is reminded of the proper format for amendments to the claims. Specifically, the claims being amended must be submitted with markings to indicate the changes that have been made relative to the immediate prior version of the claims. The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. See MPEP 714.

8. The amendments to claims 3 and 28 are not in compliance with 37 CFR 1.121 because claim 3 includes the words "the plurality of" in underlined text, which would suggest that the words have been inserted by amendment; however, the word "the" previously appeared in the prior version of the claim and should therefore not appear in underlined text.

9. The amendments to claim 28 are not in compliance because double brackets have been used to indicate the deletion of the word "obtaining" in line 4, which is improper because double brackets should only be used to show deletion of five or fewer consecutive characters.

Information Disclosure Statement

10. Applicant's Information Disclosure Statements filed 10/18/04, 11/3/04, 11/28/05, 7/24/06, and 11/16/06 have been received and entered into the application. The references therein have been considered by the examiner as indicated on the attached form PTO-1449.

11. The information disclosure statement filed 7/24/06 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because it fails to fulfill the content requirements for an IDS. Each publication listed in an information disclosure statement must be identified by publisher, author (if any), title, relevant pages of the publication, date, and place of publication.

Specifically, the reference by Mathaeus et al. entitled "Co-Regulation of Neutrophil..." has not been considered by the Examiner because the citation does not identify the publisher or date of publication. The journal name provided for the publication also appears to be incomplete.

It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

12. The information disclosure statement filed 11/28/05 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered.

Specifically, foreign patent document WO 2004/005540 (Metagen Pharmaceuticals GMBH) has been considered only to the extent of the English abstract because no explanation of relevance was provided.

13. The information disclosure statement filed 11/28/05 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Specifically, the non-patent literature publication by Vinayak et al. was not considered because only the first three lines of text are legible in the copy provided; a legible copy of the entire abstract has not been provided.

14. The U.S. Patent document US 6,447,989 (Comper et al.) has been lined through on the IDS of 11/28/05 to avoid duplicate citation, as it was previously cited on the IDS of 11/3/04. The document has been considered by the Examiner.

15. The IDS of 11/16/2006 lists a non-patent literature publication by Devarajan et al. ("Novel biomarkers for the early prediction...", 2005) and lists pages 477-488. However, because page 486 was not included in the copy of the reference submitted, only pages 477-485 and 487 of the article were considered by the Examiner.

16. Applicant is reminded that the listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have also been cited on an IDS or by the examiner on form PTO-892, they have not been considered.

Priority

17. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(3) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/458,143, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

Provisional application No. 60/458,143 discloses methods for detecting *ischemic* renal injury, while the instant claims encompass both ischemic renal injury and nephrotoxic injury (see for example the preamble of claim 1). One skilled in the art would not envisage possession of methods of detecting all types of renal tubular cell injury (e.g., nephrotoxic injury) based on the disclosure of the prior-filed application relating only to ischemic types of injury.

Accordingly, the instant claims are not entitled to the benefit of the filing date of Application No. 60/458,143.

Specification

18. There is a typographical error of the word "Blotting" at page 27, the last paragraph.

19. In line 5 of the abstract it appears that the words "appearance" and "NGAL" should be separated by the preposition "of".

20. The use of trademarks (SuperScript™, Microcon™, GenePix™, Triton™) has been noted in this application. They should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

21. Claims 2-5, and 9-11 are objected to because of the following informalities:

22. Claims 2-5, and 9-11 are objected to because ***all dependent claims should be grouped together with the claim or claims to which they refer to the extent practicable***. See MPEP 608.01(m)-(n). Specifically, the claims have been currently amended so that they depend from claims 30 or 31, but they appear in the claim set just after claim 1 and before claim 30. Although a dependent claim may refer to any ***preceding*** independent claim, in the instant case the dependent claims refer to a ***subsequent*** independent claim, which is improper.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

23. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

24. Claims 1-5, 9-11, 28, 30-40, and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

25. Independent claims 1, 30, and 46 (see the amendments filed 3/21/07) recite that the mammalian subject "is suspected of having or [is] ***prone to develop a renal tubular cell injury***" (emphasis added). Claim 34 further refers to an event that "causes the mammalian subject to have, ***or be prone to developing, the renal tubular cell injury***" (emphasis added).

Applicant's reply of 3/12/07 indicates that support for the noted limitation is supported in the specification at paragraphs 38, 45, and 101 (Reply, page 10).

The examiner notes that support for subjects *suspected of having a renal tubular cell injury* was found in the specification, for example at paragraph 15. However, support could not be found in the specification for the limitation that the mammalian subject is "prone to developing a renal tubular cell injury" or for events that cause such subjects to be prone to developing a renal tubular cell injury.

In particular, it is noted that the claimed patient population of subjects "prone to develop" renal tubular cell injury would also encompass, for example, subjects with a genetic tendency or condition that predisposes to various kidney diseases. Such patient populations are not described in the original disclosure, and therefore, the instant amendments and new claims to recite subjects "prone to developing a renal tubular cell injury" go beyond the scope of the disclosure and claims as originally filed.

The specification at paragraph 38 discloses "patients who are at risk of developing [acute renal failure]". However, since *acute renal failure* is narrower in scope that the claimed genus relating to all *renal tubular cell injury*, the noted passage does not adequately support the claimed subject matter because it is not commensurate in scope. Similarly, the specification at paragraph 45 relates only to subjects prone to, or having developed, acute renal failure.

Paragraph 101 discloses "fifteen patients after open heart surgery", which does not convey evidence of possession of the claimed population of all mammalian subjects suspected of having or being prone to develop a renal tubular cell injury as claimed.

With respect to claim 34, although the specification for events that *cause* renal tubular cell injury (see paragraphs 14, 42, and original claim 24 in particular), support could not be found for events that cause subjects to be *prone to developing* renal tubular cell injury as currently claimed.

26. New claims 36-38 also represent new matter for the following reasons. Claim 36 (added by amendment on 3/12/07) recites an **event** that "makes the mammalian subject develop or be prone to develop acute renal failure". Applicant's reply indicates that support may be found in

paragraphs 38, 42, and 48. Paragraph 38 discloses **patients** who are at risk of developing ARF (see the second sentence) but does not disclose **events** that cause or cause tendency to develop ARF. Paragraph 42 refers to a number of events including diminished blood supply to the kidneys, or administration of radiocontrast dyes.

However, such events are not described in the specification as those that "[make] the mammalian subject develop or be prone to develop acute renal failure". As such, the currently claimed genus differs in scope from that disclosed in the specification.

More particularly, new claims 36-38 depend from claim 35, which recites that urine samples are obtained *at specific times in relation to the claimed events*. Support could not be found in the specification for methods of evaluating renal tubular cell injury status that include obtaining urine samples as the specific times recited in relation to the claimed events.

Furthermore, with respect to claim 37, support could not be found in the specification or claims as originally filed for the claimed methods in which samples are obtained within 6 hours, 4 hours, 2 hours, 1 hour, or 30 minutes of "coronary bypass surgery". This term could not be found in the specification. Support could also not be found for the event of "cardiovascular surgery".

Although "vascular surgery" is disclosed at paragraph 63, this is in context of "patients with subtle, subclinical renal tubular cell injuries"; there is no mention of "evaluating renal tubular cell injury status" using urine samples obtained within 6 hours, 4 hours, 2 hours, 1 hour, or 30 minutes of vascular surgery.

Although stroke, trauma, sepsis and dehydration are disclosed at paragraph 38, there is no disclosure of methods in which urine samples are obtained at the claimed times in relation to

such events, or in particular in relation to the ***onset of*** such events as now claimed. At best, paragraph 38 conveys that the method could be used to diagnose acute renal failure in patients with sepsis; however, there is no description of such a method in which a urine sample is obtained *within 30 minutes of onset of sepsis*, for example.

In addition, although paragraph 38 discloses kidney transplantation, cardiac surgery, stroke, trauma, sepsis, and dehydration, this is in reference to **patients** who are at risk of developing acute renal failure. In particular, there is no mention of the noted subject matter as being "events" or of urine samples being taken in reference to same.

New claim 38 recites that the event "is one that causes the admission of the mammalian subject to an intensive care unit". Although paragraph 42 mentions "patients in intensive care units", support could not be found for the instantly claimed methods involving urine samples obtained at the recited times in relation to the ***admission*** to an intensive care unit.

27. Claims 34-35 also represent a departure from the specification and claims as originally filed for the following reasons. The new claims (added by amendment on 3/21/07) recite that the urine sample is obtained "within 24 hours" after an event (claim 34) or alternatively "within...6 hours, 4 hours, 2 hours, 1 hour, and 30 minutes" (claim 35).

Applicant's reply indicates that the claims as supported by the specification at paragraphs 17, 22-25, 39, and 44.

However, paragraph 17 relates to detection of RNA and not to detection of NGAL (a protein). Paragraphs 22-25 relate to experiments performed to detect NGAL in urine of mice or rats with ischemic ARF or subclinical renal ischemia. However, such specific disclosures are not

commensurate with the scope of the claims, which are not limited to ischemic renal injury or to subjects that are rodents. In addition, although paragraphs 22-25 describe obtaining urine samples at various times in relation to reperfusion after artery clamping, the instant claims are not limited to samples obtained after this type of event.

Furthermore, although paragraphs 22-25 refer to Figures 4-6, which depict the results of the experiments in terms of reperfusion periods of 0, 2, 4, 6, 8, 12, and 24 hours, the experiments do not disclose the claimed ranges involving time periods "***within*** 24 hours" or "***within***...6 hours, 4 hours, 2 hours, 1 hour, and 30 minutes". Furthermore, the time periods depicted in Figures 4-6 do not include time periods of 1 hour or of 30 minutes as recited in claim 35.

Paragraph 39 indicates that NGAL "can appear in the urine within 2 hours of the onset of renal tubular cell injury" or "within the first 24 hours of the onset of renal tubular cell injury". However, it is noted that the time periods are described in terms of the onset of injury, while the instant claims refer to time periods in relation to events that cause or predispose to injury. This conveys a different scope since an "event" that causes renal tubular cell injury may not actually result in immediate onset of injury (as for example, oral administration of a nephrotoxic drug). As such, the incorporation of the time periods "within 2 hours" and "within the first 24 hours" into the claims without their appropriate context goes beyond the scope of the original disclosure.

Similarly, paragraph 51 of the specification mentions detecting a biomarker within "about 30 minutes" or within 1, 2, or 4 hours, such time periods are also mentioned as being in reference to renal tubular cell injury.

Paragraph 44 describes sampling intervals, i.e. every 24 hours, every 4 hours, or every 30 minutes. However, such disclosure does not adequately support the instant claims since there is no mention of a point of reference in this context. The noted passage simply refers to the spacing between when samples are collected, but does not describe sampling in relation to times after an event that causes a subject to have or be prone to developing renal tubular cell injury.

28. New claim 39 recites that the method is used "to predict, diagnose, monitor, or determine the likelihood of a renal tubular cell injury". Applicant's reply indicates that the new claim is supported in Examples 4-6 and in Figures 9-16 (Reply, page 11). However, support could not be found for the claimed subject matter. Initially, it is noted that the data presented in Examples 4-6 and depicted in Figures 9-16 relates to specific experiments performed. While such experiments provide supporting data regarding the validation of NGAL as a biomarker for detection of renal tubular cell injury, they do not clearly describe using the claimed method "to predict, diagnose, monitor, or determine the likelihood of a renal tubular cell injury" in the manner now generically claimed. As such, the passages do not adequately provide support for the new claim, which is drawn generically to prediction, diagnosis, monitoring, or determining the likelihood of injury.

In particular, support could not be found for *predicting* renal tubular cell injury or for methods of *determining the likelihood* of renal tubular cell injury.

29. Claim 28 (see the amendments of 3/21/07) now recites that the urine sample is obtained "within 24 hours of an event that causes renal tubular cell injury". Applicant indicates that the amendments are supported by the specification at paragraphs 39 and 45-56 (Reply, page 10).

However, as also discussed above with respect to claims 34-35, the specification does not provide adequate support for the noted limitation. Paragraph 39 discloses that a biomarker "can appear within the first 24 hours of the onset of renal tubular cell injury" but does not mention ***collecting a urine sample*** in such a time period.

In addition, the limitation of "within 24 hours" is disclosed in reference to the onset of renal tubular cell injury, while claim 28 refers to "within 24 hours of an event that causes renal tubular cell injury". This conveys a difference in scope since an event that causes injury would not necessarily produce instantaneous onset of injury.

Paragraph 51 mentions detecting a biomarker in a urine sample within various time periods (none of which are 24 hours, however) in relation to the renal tubular cell injury and not in relation to an event that causes renal tubular cell injury as claimed.

In summary, the specification does not provide blaze marks nor direction for the instant methods encompassing the above-mentioned limitations, as currently recited. The instant claims now recite limitations that were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

30. New claim 40 recites a method wherein the NGAL level is "contrasted with a urinary NGAL level that distinguishes a mammalian subject that has a renal tubular cell injury from a mammalian subject that does not have a renal tubular cell injury". Support could not be found for the noted limitation where indicated by Applicant. Applicant's reply refers to Examples 4-6 and

Figures 9-16 (Reply, page 11). However, the noted passages refer to specific, detailed experiments and do not provide blaze marks or direction to the instantly claimed limitation.

The specification does not clearly disclose urinary NGAL levels "that distinguish a mammalian subject that has a renal tubular cell injury from a mammalian subject that does not have a renal tubular cell injury" (such as threshold levels) as such, or provide examples of what such levels would be. One skilled in the art cannot envisage possession of methods of comparing urinary NGAL levels to such distinguishing levels in the absence of any clear mention or indication of what values would be considered to distinguish the healthy and disease populations.

31. Claims 2-5, 9-11, 28, and 30-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of detecting renal tubular cell injury, does not reasonably provide enablement for all methods of "**evaluating renal tubular cell injury status**". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The nature of the invention relates to the identification and validation of NGAL as a biomarker of renal tubular cell injury, including ischemic renal injury and nephrotoxic renal injury. The elected invention is drawn to diagnostic methods of detecting renal tubular cell injury by measuring the level of NGAL in urine samples.

Independent claim 30 recites a method for "evaluating the renal tubular cell injury status" of a mammalian subject. The term "evaluating renal tubular cell injury status" would clearly encompass not only the elected invention of a method for detecting renal tubular cell injury (as in

claim 1) but also methods of predicting, monitoring, determining the likelihood of injury, determining the extent of injury, and monitoring the effectiveness of a treatment for renal tubular cell injury (see claims 39-45). Similarly, claim 28 as amended also refers to "evaluating the renal tubular cell injury status" of a subject.

The specification does not provide a specific or limiting definition for this term. As such, the claims are extremely broad with respect to what steps or processes would be considered to represent evaluating injury status.

For example, "evaluating the renal tubular cell injury status" would also refer, for example, evaluating a renal tubular cell injury so as to determine the cause of the injury. However, the specification contains no direction or guidance with regard to how NGAL detection in urine can be used to determine the cause of a renal injury. The specification discloses that NGAL is elevated in urine following a number of very different physiological conditions, including induced ischemia (Examples 1-2), renal nephrotoxemia (Example 4), kidney transplantation (Example 5), and open heart surgery (Example 6). However, there is no indication that elevation of NGAL might be used to determine the underlying pathophysiology that has resulted in renal injury.

Furthermore, "evaluating the renal tubular cell injury status" would also encompass various prognostic methods, for example, use of NGAL levels to predict likelihood of a patient recovering, prediction of risk of recurrence of disease, prediction of risk of mortality, etc. The data and guidance presented specification are simply insufficient to enable the skilled artisan to carry out such methods.

For example, in the absence even of any data to suggest that NGAL levels might be correlated with future risk of mortality (for example), one skilled in the art would face an undue burden of examination given the laborious and lengthy nature of biomarker validation recognized by those skilled in the art.

For example, Bast et al. ("Translational Crossroads for Biomarkers" Clin Cancer Res 2005; 11(17), 6103-6108) point to the "lengthy process" of assay development and validation and note that many markers that correlate with disease statistically may not prove to be useful clinically (p. 6105, right column). See also LaBaer et al. ("So, You Want to Look for Biomarkers" Journal of Proteome Research 2005; 4, 1053-1059), which teaches that crucial validation steps are needed to demonstrate that an identified biomarker is a reliable predictor, and also that the process of converting such a biomarker into a practical clinical test is even more daunting (p. 1053, see the paragraph bridging the left and right columns). Baker ("In Biomarkers We Trust?" Nature Biotechnology 2005; 23(3), 297-304) also speaks to the unpredictability involved in clinically applying biomarkers (see p. 298, the section "Walking on Thin Ice"):

"Using a new biomarker is like walking across a frozen lake without knowing how thick the ice is," says Ole Vesterqvist..."You start walking, and you get comfortable. Then you break through."

Thus, the state of the art teaches the unpredictability associated with the clinical use of biomarkers even after a biomarker has been correlated with a specific disease state.

One cannot extrapolate the teaching of the specification to the scope of the claims because said teachings represent insufficient guidance and objective evidence to predictably enable the use of the claimed invention.

In summary, due to the breadth of the subject matter encompassed by the term "evaluating the renal tubular cell injury status", and to the lack of direction/guidance presented in the specification in a manner commensurate with such scope, the specification fails to teach the skilled artisan how to make and use the claimed invention in its full scope without undue experimentation.

32. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

33. Claims 1, 28, 33, 40 and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

34. Claims 1, 28, and 46 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: method steps and/or correlation steps in the body of the claim that clearly relate back to the method objectives as recited in the preamble.

Claims 1 and 46 recite methods for the "detection of a renal tubular cell injury"; however, the claims conclude with the step of detecting an antibody-NGAL complex. As such, there are no active method steps in the claims that achieve the objective of detecting injury as recited in the preambles. Alternatively, a correlation step may be employed that clearly describes how the results of the assay relate back to the method objective.

Similarly, claim 28 recites a method for the detection of a renal tubular cell injury; however, the claim concludes with the broad step of "evaluating the renal tubular cell injury

status", which would not necessarily achieve the specific objective of detecting renal tubular cell injury. As such, the claim lacks a step that clearly relates back to the method objective as recited in the preamble.

35. Claim 33 recites the limitation "the onset of renal tubular cell injury" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim.

36. Claim 40 recites that the NGAL level is contrasted with "a urinary NGAL level that distinguishes a mammalian subject that has a renal tubular cell injury from a mammalian subject that does not have a renal tubular cell injury". However, the metes and bounds of the claim are unclear because the specification does not define or clearly exemplify what value or values of NGAL levels would be considered to distinguish normal vs. disease subjects (see also new matter rejection above). Consequently, one skilled in the art would not know based on the specification whether a particular NGAL level would fall within the scope of the claim or not.

Claim Rejections - 35 USC § 102

37. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

38. Claims 1-2, 28, 30-37, 39-40, and 46 are rejected under 35 U.S.C. 102(a) as being anticipated by Mishra et al. ("Identification of Neutrophil Gelatinase-Associated Lipocalin as a Novel Early Urinary Biomarker for Ischemic Renal Injury," *J Am Soc Nephrol* 14 (October

2003), 2534-2543, see Applicant's IDS of 10/18/04). It is noted that the reference constitutes prior art under 102(a) because all claims under examination are not entitled to the benefit of the filing date of provisional application 60/458,143 for the reasons noted above under ***Priority***.

Mishra et al. teach that urinary NGAL is an early, sensitive, and noninvasive biomarker for ischemic and nephrotoxic injury (see especially the abstract and page 2542). In particular, the reference teaches obtaining a urine sample from a mammalian subject suspected of having or being prone to develop a renal tubular cell injury, in that urine samples were obtained from rats subjected to renal ischemia-reperfusion injury by artery clamping (page 2535, "Rat Model of Renal Ischemia-Reperfusion Injury"; p. 2536, "Urine Collection"; p. 2536-2537, in particular the sections "Characterization of the Animal Models..." and "NGAL Protein is Markedly Overexpressed..."; and p. 2538). Additional experiments were performed for a mouse model of nephrotoxic renal injury induced by administration of cisplatin (p. 2535, "Mouse Model of Cisplatin-Induced Renal Injury"; p. 2540, "NGAL Protein is Easily Detected...").

With respect to claims 1 and 31, detection of NGAL in the urine sample was performed by Western blotting, which involved contacting the urine sample with a polyclonal antibody to NGAL and detecting the antibody-NGAL complex by chemiluminescence (see p. 2536, "Urine Colllection" and "Other Materials and Methods"; page 2538, the three sections beginning "NGAL Protein is Easily Detected in the Urine..."; and Figures 5-7).

With respect to claims 28 and 30, the reference teaches correlating the renal tubular cell injury status of the subjects with elevated NGAL levels, which would read on the broadly claimed step of "evaluating the renal tubular cell injury status of the subject".

In summary, the reference teaches that NGAL is upregulated after renal injury (ischemia or cisplatin-induced injury), such that it may be used as a biomarker for ischemic and nephrotoxic renal injury to allow for early diagnosis of renal tubular cell injury (p. 2542, right column; see also p. 2537-2539 at the sections "NGAL mRNA is Markedly Induced...", "NGAL Protein is Markedly Overexpressed...", and "NGAL mRNA is Induced in Cultured Human Proximal Tubule Cells..."; and p. 2540-2542, "Discussion", especially at p. 2541, right column, the first full paragraph and p. 2542, right column).

With respect to claim 2, Mishra et al. teach intermittent samples of urine obtained at various time points (p. 2535, left column, last paragraph; and right column, first paragraph).

With respect to claims 28 and 33-37, Mishra et al. teach assaying for NGAL within 2 hours of ischemic injury, in the very first urine output (see the abstract; p. 2538 and Figure 5). Given the broadest reasonable interpretation, the renal artery occlusion procedures performed with microvascular clamps (page 2535, left column, last paragraph) would be considered to be "vascular surgery".

Also with respect to claim 28, the reference teaches detection of NGAL in a as little as 1 microliter of urine (page 2538, the paragraph bridging the left and right columns; right column, at the first full paragraph; and Figures 5-6).

With respect to claim 39, Applicant is reminded that claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. See MPEP 2111.04. In the instant case, the claim recites that the method "is used to predict, diagnose, monitor or determine the

likelihood of a renal tubular cell injury" but does not require any additional steps to be performed. As such, the reference reads on the claims.

Furthermore, given the broadest reasonable interpretation, the studies of NGAL as an early biomarker of renal injury performed by Mishra et al. would be considered to represent methods of "monitoring" renal tubular cell injury, in that the authors monitored NGAL expression over the course of the disease.

With respect to claim 40, the reference teaches comparing NGAL levels with levels in urine prior to injury, and report that before ischemia NGAL was absent.

39. Claims 1 and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Venge et al. (US 6,136,526) in light of the evidence of iHOP (Information Hyperlinked over Proteins, entry for "LCN2", retrieved from http://www-ihop-net.org/UniPub/iHOP/gs/89799.html on 5/18/07) and Potempa (US 5,405,832).

Venge et al. teach methods of diagnosing human disease by measuring the level of HNL in sample from a subject such as urine (see in particular the abstract and column 1, line 50 to column 2, line 26).

iHOP is cited as an evidentiary reference for its list of various other names by which NGAL is also known in the literature, including HNL (see top, the sections "Symbol", "Name", and "Synonyms"). Thus, in light of the evidence of iHOP it is apparent that the protein referred to by Venge et al. as "HNL" is a synonym referring to the same protein, NGAL.

Venge et al. further teach assaying for NGAL in human patients with clinically diagnosed acute bacterial or viral infections, including patients with pneumonia, acute upper urinary tract infections, pleuritis, and septicaemia (column 8, line 27 to column 9, line 20).

Such subjects are "suspected of having or being prone to develop a renal tubular cell injury" as claimed in light of the evidence of Potempa, which teaches that "septicemia" is also referred to as "sepsis" (column 1, lines 10-20). The instant specification indicates that patients with sepsis are at risk of developing acute renal failure ([0038]), such that septicaemia subjects of Venge et al. read on the claim limitation since they are at risk of developing acute renal failure, which is a type of renal tubular cell injury.

Venge et al. further teach that NGAL is preferably assayed by immunoassay, in which the sample is contacted with an antibody specific for NGAL and detecting the immune complex formed (column 2, line 27 to column 3, line 60).

With respect to the preambles of the claims, which refer to a "method for the detection of a renal tubular cell injury", it is noted that the statements appearing in the preamble do not provide antecedent basis for terms in the body of the claim and are not essential to understand the limitations or terms in the claim body. Furthermore, the bodies of the claims do not contain any active method steps that clearly relate back to the preambles. While the preamble conveys the purpose or intended use of the claimed invention, such statements merely define the context in which the invention operates and usually will not limit the scope of the claim (MPEP 2111.02 and DeGeorge v. Bernier, Fed. Cir. 1985, 226 USPQ 758, 761 n.3).

In the instant case, although Venge et al. relates to the use of NGAL as a diagnostic marker for discriminating between bacterial and viral infection, since the reference teaches all

active method steps relating to detection of NGAL in samples (which may be urine) in the same patient population as claimed, the reference is anticipatory since there are no steps recited in the claims in which renal tubular cell injury is actually detected in a mammal.

Claim Rejections - 35 USC § 103

40. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

41. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

42. Claims 5, 30, and 32-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matthaeus et al. ("Acute Ischemic Renal Failure Induces Expression of Neutrophil Gelatinase-Associated Lipocalin and Matrix Metalloproteinase-9 in Damaged Tubuli" *Kidney Blood Press Res* (2001), Vol. 24, page 342, abstract No. P268, Applicant's IDS of 7/24/06) in view of Gold et al. (US 6,242,246 B1), Ramsden et al. (US 4,640,909), Blaser et al. ("A sandwich enzyme immunoassay for the determination of neutrophil lipocalin in body fluids" Clin Chim Acta. 1995

Mar 31;235(2):137-45, Applicant's IDS of 7/24/06), and Moses et al. (US 7,153,660 B2), or in the alternative over Matthaeus et al. and Ohlsson et al. ("Increased circulating levels of proteinase 3 in patients with anti-neutrophilic cytoplasmic autoantibodies-associated systemic vasculitis in remission" Clin Exp Immunol. (available online February 28, 2003) 131(3):528-35, see Applicant's IDS of 7/24/06) in view of Gold et al., Ramsden et al., Blaser et al., and Moses et al.

Matthaeus et al. teach that levels of NGAL protein are upregulated in response to ischemic renal injury in a rat model (see entire selection). By contrast, control animals displayed only minor expression of NGAL, demonstrating that renal injury and repair is associated with an upregulation of NGAL. Such experiments read on the claimed step of "evaluating the renal tubular cell injury status" as recited in claim 30 since given the broadest reasonable interpretation, the investigation and correlation of renal injury status (i.e., control or postischemic subject) with levels of expressed NGAL over time by Matthaeus et al. would be considered to represent "evaluation" of renal injury status.

The reference differs from the claimed invention in that Matthaeus et al. fail to specifically teach detecting NGAL in **urine** as claimed.

It was well known in the art that disease processes may produce changes in the levels of certain specific analytes, and that measurement of the levels of such analytes can be used to detect the presence of the disease.

As just one example, Gold et al. teach that changes in the levels of certain target molecules (e.g. those not normally found in healthy individuals but known to present in diseased

individuals) can be detected in samples from individuals at risk of the disease for the purpose of diagnosis (column 2, line 15 to column 3, line 25).

Therefore, it would have been obvious to one of ordinary skill in the art detect NGAL for the purpose of diagnosing renal injury in light of the teachings of Matthaeus et al. that NGAL is specifically elevated in this disease condition, and further in view of the general knowledge of one skilled in the art that markers changed in response to disease can be used as biomarkers for diagnosis of the disease (as taught for example by Gold et al.).

Mattheus et al. also make clear that the rat studies were performed as an animal model of disease. Given such a teaching, it would have been obvious to detect NGAL in human subjects for the clear benefit of diagnosing human disease. In such a case, it would have been further obvious to employ urine as the sample source, rather than the kidney tissue samples examined in the rat model of Matthaeus et al., for the following reasons.

Initially, it is noted that one skilled in the art would immediately recognize that isolation of kidney tissue would be very invasive, and therefore unsuitable method for diagnosing renal injury in humans.

Alternative sources of samples for biomarker detection were known in the art; specifically, it was well known to one skilled in the art of biochemical assay at the time of the invention that urine is a non-invasive and easily collected type of sample.

See for example Ramsden et al., column 1, lines 15-16, which teaches that urine samples are noninvasive and convenient.

Therefore, in light of the general knowledge of one skilled in the art that urine is an easily collected and non-invasive sample source for assay of biological analytes (as taught for example

by Ramsden et al.), it would have been obvious to use urine as the sample source instead of the kidney tissue samples when detecting NGAL for diagnosis of renal injury in human subjects, for the advantage of being a non-invasive and easily collected sample.

One would have a reasonable expectation of success because it was known in the prior art that NGAL is excreted in urine, as taught by Blaser et al. and Moses et al.

Blaser et al. teach detection of human neutrophil lipocalin (NGAL) in urine by sandwich ELISA (see in particular the abstract; page 139, section 2.4; and pages 142-143, sections 3.3-3.4).

Moses et al. also teach that NGAL may be detected in human urine by Western Blot (Example 2 and Figure 1B).

As such, in light of the teachings of Blaser et al. and Moses et al., one skilled in the art would have a reasonable expectation of success in using urine as a sample source for detection of NGAL in response to renal injury (rather than kidney tissue as taught by Matthaeus et al.) since NGAL was known to be excreted in urine.

With respect to the combination of the Matthaeus et al., Ohlsson et al., Gold et al., Ramsden et al., Blaser et al., and Moses et al. references, it is noted that Ohlsson et al. adds additional evidence that NGAL was known to be elevated in renal injury.

Specifically, Ohlsson et al. teach an ELISA method to detect NGAL (p. 530, left column; p. 531, the section "PR3 versus neutrophil activation and degranulation"; Figures 3-4; and Table 4b in particular). The reference teaches the steps of obtaining a blood plasma sample from a mammalian subject; it would seem that all mammals are "at risk" of developing a renal injury as recited. However, Ohlsson et al. specifically looked at patients with ANCA-associated systemic

vasculitis and recorded development of renal failure (p. 529 "Patient material"). The reference further teaches evaluating the renal tubular cell injury status based on the level of NGAL in that Ohlsson et al. teach that ***greatly elevated NGAL levels are strongly correlated with decreased renal function*** (p. 531, the left column, last paragraph). Given the broadest reasonable interpretation of "evaluating the renal tubular cell injury status", the correlating of NGAL levels with renal failure status by Ohlsson et al. meets the limitation.

Taken together with the findings of Matthaeus et al., it would have been obvious to detect NGAL for the purpose of diagnosing renal dysfunction since the references establish that NGAL is specifically elevated in this disease condition, and further in view of the general knowledge of one skilled in the art that markers changed in response to disease can be used as biomarkers for diagnosis of the disease (as taught for example by Gold et al.).

Although neither Matthaeus et al. nor Ohlsson et al. examined NGAL levels in urine (Ohlsson et al. employed blood plasma), it would have been obvious to use urine as the sample source instead of the kidney tissue samples when detecting NGAL for diagnosis of renal injury in human subjects, for the advantage of being a non-invasive and easily collected sample (as taught by Ramsden et al.).

One would have a reasonable expectation of success because it was known in the prior art that NGAL is excreted in urine, as taught by Blaser et al. and Moses et al.

With respect to claim 5, as noted above, one would be motivated to detect NGAL in humans for the purpose of diagnosing human disease. One would have a reasonable expectation of success because Matthaeus et al. clearly indicates that detection of NGAL in rats was done as an animal model, i.e. an animal model of human disease, and further because Ohlsson et al.,

Moses et al. and Blaser et al. teach that NGAL is also expressed in humans. The Ohlsson et al. reference also establishes that NGAL levels in humans are correlated with renal dysfunction.

With respect to claim 33, it is noted that the claim recites a method "wherein the method is used to detect NGAL present in the first urine output of the subject...". This language suggests, but does not clearly require, that the urine sample is one that is taken immediately after the onset of renal tubular cell injury. There are no method steps recited in the claim that definitively require that the urine sample assayed as per claim 30 is one which is taken in the first urine output. See MPEP 2111.04. Consequently, the claim language may also be interpreted as merely indicating, for example, one possible application or intended use of the invention, such language is not considered to be limiting and therefore, the references read on the claim.

43. Claims 1, 4, 9-11, 28, 31, 34-36, 39-40, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matthaeus et al. in view of Gold et al., Ramsden et al., Blaser et al., and Moses et al., or in the alternative over Matthaeus et al. and Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al., and Moses et al. as applied to claims 5, 30, and 32-33 above, and further in view of David et al. (US 4,376,110).

The references are as discussed above. With respect to independent claims 1 and 46, which refer to "detection of a renal tubular cell injury in a mammal", it is noted that the claims do not include any steps that achieve such an objective, and therefore, the preamble is not found to further limit the claim.

Nonetheless, it is noted that even should the preamble be considered to further limit the method, the claimed invention is nonetheless obvious over the references for the reasons

discussed in further detail above. In particular, Matthaeus et al. and Ohlsson et al. teach that NGAL levels correlate with renal function. Taken together with the general knowledge of one skilled in the art that markers changed in response to disease conditions can be used as biomarkers for diagnosis of disease (as taught for example by Gold et al.), it would have been obvious to detect NGAL levels for the purpose of diagnosing renal tubular cell injury, as discussed in detail above. It would have been further obvious to detect NGAL in urine, given that urine is a non-invasive source of sample (as taught by Ramsden et al.) and because NGAL was known to be excreted in urine (as taught by Blaser et al. and Moses et al.).

The instant claims differ in that they relate to antibody-based detection of NGAL, where NGAL is detected by contacting the urine sample with an antibody to NGAL and detecting the antibody-NGAL complex.

However, immunoassays, including those involving a primary "capture" antibody and secondary labeled antibody in a "sandwich" immunoassay format, were well known in the art to be sensitive and rapid means of detecting analytes in samples.

For example, David et al. teach sandwich or "two-site" immunoassays for detecting the presence of analytes in fluids, in which an unlabeled "capture" antibody is bound to a media (solid support) and then contacted with a sample containing the analyte (see in particular the abstract; column 3, line 10 to column 6, line 61, and especially column 4, lines 19-37). After formation of a capture antibody-analyte complex, a second labeled antibody is added which recognizes a different site on the analyte, resulting in the formation of a "sandwich" (see especially column 1, line 47 to column 2, lines 17; column 5, lines 45-60). This type of assay format has great utility in detecting the presence or amount of an analyte, and the improvements

reported by David et al. also produce an assay format that is rapid and sensitive while eliminating false positive results (column 8, lines 33-38; and also column 1, line 67 to column 2, line 7).

Therefore, it would have obvious to one of ordinary skill in the art to detect NGAL in the method of Matthaeus et al., Gold et al., Ramsden et al., Blaser et al., and Moses et al., or alternatively in the method of Matthaeus et al., Ohlsson et al., Gold et al., Ramsden et al., Blaser et al., and Moses et al. using the well known sandwich immunoassay format, e.g. as taught by David et al. One would be motivated to employ this method to detect the presence of NGAL because it is well recognized in the prior art to be a rapid and sensitive method of detecting analytes in a fluid sample.

With respect to claims 10-11, the method of David et al. involves contacting the fluid sample with the media (solid phase) upon which the primary antibody has been immobilized (see for example column 1, lines 47-56; column 6, lines 5-17; and the Example).

With respect to claims 28 and 34-36, Matthaeus et al. teach that NGAL was elevated "after 24 and 48 hours" of ischemia as detected by Western blot. However, it would have been obvious to one of ordinary skill in the art to detect NGAL levels "within 24 hours" out of the normal desire of artisans to improve upon what is already known. See MPEP 2144.05.

In particular, one would be motivated to detect NGAL within 24 hours or earlier in order to diagnose disease earlier, and therefore to allow for timely interventions to be performed. One would have a reasonable expectation of success because the immunoassay method of David et al. is more sensitive, such that upregulation of NGAL would be reasonably expected to be detectable at earlier time points than by Western blot (as performed by Matthaeus et al.).

In addition, it would have been obvious to employ a sample size of "up to 1 milliliter" as in claim 28 given that sample size was recognized in the prior art as a result-effective variable, for example when employing test strip devices for detecting analytes. As such, it would have been a matter of routine optimization to select a suitable volume of urine for assay within the claimed range.

With respect to claim 40, Matthaeus et al. teach comparison of NGAL levels in control and disease subjects and reported that only minor expression of NGAL was seen in control animals (see right column). The minor expression levels of NGAL would therefore be considered to distinguish the subjects with the renal tubular cell injury from those without.

44. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Matthaeus et al. in view of Gold et al., Ramsden et al., Blaser et al., and Moses et al., or in the alternative over Matthaeus et al. and Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al., and Moses et al. as applied to claim 30 above, and further in view of Valkirs et al. (US 2003/0109420 A1).

The references are as discussed above, which teach a method for detecting NGAL in a urine sample substantially as claimed, but which fail to specifically teach that the urine sample comprises a plurality of urine samples that are obtained intermittently or continuously.

Valkirs et al. teach that one skilled in the art would recognize the value of testing multiple samples (for example, a series of samples obtained at successive time points) from the same individual, e.g. in allowing identification of changes in levels of markers over time [0107]. Such data can provide information about disease status, including appropriateness about drug therapies and identification of patient outcome.

45. Claims 2-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matthaeus et al. in view of Gold et al., Ramsden et al., Blaser et al., and Moses et al., or in the alternative over Matthaeus et al. and Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al., and Moses et al., as applied to claim 30 above, and further in view of Linzer et al. (US 3,635,091)

The references are as discussed above, which teach a method for detecting NGAL in a urine sample substantially as claimed, but which fail to specifically teach that the urine sample comprises a plurality of urine samples that are obtained continuously.

Linzer et al. teach a urine sample collector in which urine obtained by having the patient urinate continuously into the container (see especially column 1, lines 1-45 and column 2, lines 46-57). The collector separates the urine into two fractions, so that if necessary the initial urine fraction can be compared with the midstream specimen (column 2, lines 46-57). The collector can also be adapted so that the liquid can be deposited into multiple independent containers (the abstract). The reference teaches that the sample collector has the advantage in that it provides a specimen free of contamination (column 1, lines 1-73).

Therefore, it would have been obvious to obtain multiple urine samples in a continuous fashion (continuous stream of urine) using the urine specimen collector of Linzer et al. in order to ensure that the analyzed sample was free of contamination.

46. Claims 33-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matthaeus et al. in view of Gold et al., Ramsden et al., Blaser et al., and Moses et al., or in the alternative over Matthaeus et al. and Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al., and

Moses et al. as applied to claim 30 above, and further in view of Muramutsu (Kidney International, Vol. 62 (2002), pages 1601-1610, Applicant's IDS of 10/18/04).

The references are as discussed above. Matthaeus et al. teach that NGAL was elevated "after 24 and 48 hours" of renal ischemia. However, the references fail to specifically teach detection of NGAL in relation to one of the specific events recited in claims 37-38. As also discussed above, however, the references fail to specifically teach detection of NGAL "within 24 hours" or at the specified times recited in claim 35.

Muramutsu et al. teach that it is imperative to diagnose acute renal failure (ARF) as soon as possible, and that disease markers that can be measured in blood or urine would be of extreme value since ARF is associated with high morbidity and mortality (see especially page 1601).

In particular, the reference teaches screening for a biomarker of ARF (Cyr61) by detecting the presence of urinary Cyr61 within specified times in relation to the onset of induced renal ischemia, as a model of ARF (see especially pages 1603-1604, "Urine Collection"; page 1606; and Figure 8). The reference exemplifies time points of 3-6, 6-9, 9-12, 12-18, and 18-24 hours after ischemia (see especially the legend to Figure 8) and report that the levels of urinary Cyr61 were seen to increase within 3-6 hours (page 1608). The reference also teaches that no urine was produced within the first three hours, such that the first time point of 3-6 hours would represent the first urine output (legend to Figure 8).

Therefore, with respect to claims 33-36, it would have been obvious to one of ordinary skill in the art to detect NGAL levels as early as possible as taught by Muramatsu, and in particular within the recited time ranges in relation to the onset of injury out of the normal desire of artisans to improve upon what is already known. See MPEP 2144.05. In particular, one would

be motivated to detect NGAL within 24 hours or earlier in order to diagnose disease earlier, and therefore to allow for timely interventions to be performed. Given that Muramatsu exemplify time points that overlap those disclosed (e.g., 3-6 hours), it would have been a matter of routine optimization to determine and select appropriate times for urine collection based on when NGAL is increased.

With respect to claims 37-38, Muramatsu et al. further teach that the biomarker Cyr61 is rapidly induced in the kidney in response to renal ischemia, and that because of this rapid induction pattern, it may serve as an early disease marker for renal injury (see the paragraph bridging pages 1608-1609). The reference further indicates that the marker could be used in a variety of settings including after contrast administration, chemotherapy, transplantation, vascular surgery, or in kidney donors, or with multi-organ failure in the ICU.

One skilled in the art would clearly appreciate the parallels between the biomarker Cyr61 as taught by Muramatsu and the NGAL protein taught by Matthaeus et al. (and also by Ohlssen et al.). Matthaeus et al. teach that like Cyr61, NGAL is upregulated in response to renal ischemia. Taken together with the teachings of Muramutsu et al. that a marker exhibiting this property may serve as an early disease marker for renal injury after transplantation or vascular surgery, one skilled in the art would be highly motivated to employ NGAL as a biomarker of renal tubular cell injury for this same purpose. As such, it would have been obvious to detect NGAL in the context of transplantation or vascular surgery for the purpose of diagnosing ARF.

With respect to claim 38, it would be immediately envisaged that such significant medical events as kidney transplantation or vascular surgery would involve admission to an intensive care unit.

Double Patenting

47. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

48. Claims 1-5, 9-11, 28, 30-40, and 46 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 11/374,285. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application recites a method of obtaining a biological fluid sample (which may be urine) from a mammalian subject (see for example claims 1-2, 10-11, and 17-18), contacting the sample with an antibody for NGAL, and detecting the antibody-NGAL complex (see claims 4-8 and 13-16). This fully anticipates the limitations and method steps recited in instant claims 1 and 30, for example. Furthermore, with respect to the preambles of instant claims 1 ("[a] method for the detection of a renal tubular cell injury") and 30 ("[a] method for evaluating the renal tubular cell injury status"), it is noted that

the copending application recites a method for *detection of worsening renal tubular cell injury* (see claim 1), which would read on both of the instantly claimed methods since detection of worsening renal tubular cell injury would be considered to represent a species reading on the instantly claimed genus of detection of renal tubular cell injury as in instant claims 1 and 46. Furthermore, detection of worsening renal tubular cell injury would also be considered a species of "evaluating" renal tubular cell injury "status" as in instant claim 30.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

49. Claims 1-5, 9-11, 28, 30-40, and 46 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2, 4, 7-10, and 22-39 of copending Application No. 11/096,113 in view of Ramsden et al., Blaser et al., and Moses et al., or alternatively in view of Mishra et al. (*J Am Soc Nephrol* 14:2534-2543, October 2003).

Copending application No. 11/096,113 recites a method for evaluation of a renal tubular cell injury in a mammalian subject (see especially claims 27 and 31) based on the level of NGAL in a sample. The level of NGAL may be determined by antibody binding (see claim 2), as recited in instant claim 1, for example.

The claims of the copending application differ from the instantly claimed invention in that in application No. 11/096,113 the sample assayed for NGAL is *blood or serum* (see claims 2, 9, and 24 in particular), while the sample assayed in the instant invention is *urine.*

However, it was well known to one skilled in the art of biochemical assay at the time of the invention that urine is a non-invasive and easily collected type of sample. See for example Ramsden et al., column 1, lines 15-16, which teaches that urine samples are noninvasive and convenient. In addition, it was known in the prior art that NGAL is excreted in urine: Blaser et al. teach detection of human neutrophil lipocalin (NGAL) in urine by sandwich ELISA (see in particular the abstract; page 139, section 2.4; and pages 142-143, sections 3.3-3.4). Moses et al. also teach that NGAL may be detected in human urine by Western Blot (Example 2 and Figure 1B).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to detect NGAL in urine rather than in blood or serum for the advantages of ease of collection associated with the non-invasive nature of urine sampling. In light of the teachings of Blaser et al. and Moses et al., one skilled in the art would have a reasonable expectation of success in using urine as a sample source for detection of NGAL in response to renal injury (rather than kidney tissue as taught by Matthaeus et al.) since NGAL was known to be excreted in urine.

Alternatively, it would have been obvious to employ urine rather than blood or serum as in the copending application because Mishra et al. (discussed above) also teach that detection of NGAL in urine is noninvasive and can be used as an early and sensitive biomarker for ischemic and nephrotoxic renal injury (see in particular the abstract).The teachings of Mishra et al. also establish a reasonable expectation of success in employing urine samples, in that the reference teaches that urinary NGAL is also a noninvasive and sensitive biomarker of renal injury.

This is a provisional obviousness-type double patenting rejection.

Conclusion

50. No claims are allowed.

51. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

52. The abstracts of the Mishra et al. and Ohlsson et al. references applied above as downloaded from the NCBI database and from the Publisher's website, respectively, have been cited to establish the public availability dates of the references, as the months of publication are not listed on the copies of the articles provided.

53. Pugh et al. (US 6,847,451 B2) teach that it was known in the prior art to assay samples of less than 1 milliliter (see for example column 17, lines 10-30).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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